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 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
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 NEWS  9  Jun 03  New e-mail delivery for search results now available
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 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 23, 2002;
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 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
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 NEWS 16  Aug 06  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 09  JAPIO to be reloaded August 25, 2002
 NEWS 20  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS 21  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 22  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 23  Aug 26  Sequence searching in REGISTRY enhanced

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
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               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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L4 117 L3 AND INFLAMMATORY AUTOIMMUNE DISEASE

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L5 41 DUP REMOVE L4 (76 DUPLICATES REMOVED)

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L6 10 L5 AND RHEUMATOID ARTHRITIS

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PROCESSING COMPLETED FOR L6
L7 10 DUP REMOVE L6 (0 DUPLICATES REMOVED)

=> d l7 1-10 chib abs

L7 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2002 ACS
2002:297615 Document No. 137:15904 Vasoactive intestinal peptide in the immune system: Potential therapeutic role in inflammatory and autoimmune diseases. Delgado, M.; Abad, C.; Martinez, C.; Juarranz, M. G.; Arranz, A.; Gomariz, R. P.; Leceta, J. (Departamento Biologia Celular, Facultad de Biologia, Universidad Complutense, Madrid, 28040, Spain). Journal of Molecular Medicine (Berlin, Germany), 8 (1 , 16-24 (English) 2002. CODEN: JMLMES. ISSN: 0946-2716. Publisher: Springer-Verlag.
AB A review. Vasoactive intestinal peptide (VIP), a neuropeptide that is produced by lymphoid as well as neural cells, exerts a wide spectrum of immunol. functions, controlling the homeostasis of the immune system through different receptors expressed in various immunocompetent cells. In the last decade, VIP has been clearly identified as a potent anti-inflammatory factor, which acts by regulating the prodn. of both

anti- and pro-inflammatory mediators. In this sense, VIP has been described to prevent death by septic shock, an acute inflammatory disease with a high mortality. In addn., VIP regulates the expression of co-stimulatory mols., this being an action that may be related to modulating the shift toward Th1 and Th2 differentiation. We have recently reported that VIP prevents the deleterious effects of an exptl. model of **rheumatoid arthritis**, by downregulating both inflammatory and autoimmune components of the disease. Therefore, VIP has been proposed as a promising candidate alternative **treatment** for acute and chronic inflammatory and autoimmune diseases such as septic shock, arthritis, multiple sclerosis, Crohn disease, or autoimmune diabetes.

L7 ANSWER 2 OF 10 MEDLINE
2001344230 Document Number: 21300949. PubMed ID: 11407385. A role for parathyroid hormone-related protein in the pathogenesis of **inflammatory/autoimmune diseases**. Funk J L.
(Department of Medicine, University of Arizona, Tucson, AZ, USA.. jfunk@u.arizona.edu) . Int Immunopharmacol, (2001 Jun) 1 (6) 1191-21.
Ref: 133. Journal code: 100969259. ISSN: 1567-5769. Pub. country: Netherlands. Language: English.
AB Our increased understanding of the critical role of cytokines in chronic **inflammatory/autoimmune diseases** has led to the recent development of effective anti-cytokine **treatments**. In particular, agents blocking the function of TNF-alpha, a cytokine first identified as an endotoxin-inducible mediator of tumor cell necrosis, are now licensed for the **treatment** of **rheumatoid arthritis** (RA) and inflammatory bowel disease. However, TNF-alpha is but one member of a cytokine network that is responsible for mediating these inflammatory disorders. Therefore, as our understanding of the pathophysiologic role of other members of this inflammatory network increases, other cytokines may similarly be identified as effective targets for **treatment**. In this article, we will review evidence which suggests that parathyroid hormone-related protein (PTHrP), a peptide which, like TNF-alpha, was first identified because of its effects in the setting of malignancy, may in fact serve an important non-neoplastic, physiologic function by mediating the inflammatory/autoimmune host response. Data identifying PTHrP as a member of the cytokine network induced in multi-organ inflammation and **rheumatoid arthritis** will be summarized, initial evidence comparing the therapeutic efficacy of PTHrP- vs. TNF-alpha-blockade in the **treatment** of endotoxemia will be reviewed, and potential future areas of research, including assessment of the effects of PTHrP blockade in the **treatment** of RA, will be discussed.

L7 ANSWER 3 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001162449 EMBASE Anti-TNF agents for **rheumatoid arthritis**
. Seymour H.E.; Worsley A.; Smith J.M.; Thomas S.H.L.. H.E. Seymour, Reg. Drug and Therapeutics Centre, Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH, United Kingdom. h.e.seymour@ncl.ac.uk. British Journal of Clinical Pharmacology 51/3 (201-208) 2001.
Refs: 33.
ISSN: 0306-5251. CODEN: BCPHBM. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB **Rheumatoid arthritis** (RA) is a chronic **inflammatory, autoimmune disease** with a prevalence of approximately 1- and an annual incidence of 0.04-. Up to 50- of patients with RA are unable to work 10 years after diagnosis. The disease is associated with significant morbidity and mortality with associated medical costs to the UK of between .pnd.240 M and .pnd.600 M per year. Non steroidal anti-inflammatory drugs (NSAIDs) have little effect on the underlying course of RA, but they have some anti-inflammatory and analgesic properties. Disease modifying

antirheumatic drugs (DMARDs) have been shown to slow progression of RA and are currently recommended early in the course of **treatment** of RA which is when disease progression is most rapid. Etanercept and infliximab belong to a new group of parentally administered antitumour necrosis factor (TNF) drugs. Etanercept is licensed in the UK for the **treatment** of active **rheumatoid arthritis** in patients who have not responded to other DMARDs and in children with polyarticular-course juvenile arthritis who have not responded to or are intolerant of methotrexate. In adults it produces significant improvements in all measures of rheumatic disease activity compared to placebo. In patients whose disease remains active despite methotrexate **treatment**, further improvement in control is obtained with the addition of etanercept without an increase in toxicity. In one small trial, etanercept was found to be more effective than placebo in a selected group of children. Infliximab is a monoclonal antibody which is currently licensed in the UK for Crohn's disease and, in combination with methotrexate for the **treatment** of **rheumatoid arthritis** in patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate. In clinical trials infliximab produced significant improvements in all measures of rheumatic disease activity compared with placebo. Infliximab in combination with methotrexate was shown to be superior to methotrexate or infliximab alone. There are currently no predictors of a good response to anti-TNF drugs and a percentage of patients fail to respond to **treatment** (25% to 38% of etanercept patients; 21% to 42% of infliximab patients). Infliximab monotherapy induces the production of anti-infliximab antibodies, which may reduce its effectiveness. Adding methotrexate to infliximab therapy may prevent this response. Anti-TNF drugs may affect host defences against infection and malignancy; whether these agents affect the development and course of malignancies and chronic infections is unknown and safety and efficacy in patients with immunosuppression or chronic infections has not been investigated. With infliximab, upper respiratory tract infections, general infections and those requiring antimicrobial **treatment** were more common in patients than placebo. Likewise, upper respiratory tract infections were more common in patients treated with etanercept than with placebo. Injection site reactions occur with both infliximab (16%-20%) and etanercept (37%). There are approximately 500 000 patients with RA in the UK, and of these between 2% and 3.5% may have severe disease which has failed to respond to conventional **treatment** and who might be eligible for anti-TNF therapy. If between 50% and 70% of patients treated with anti-TNF drugs respond and continue on long-term **treatment** then the recurrent annual cost to the NHS could be between .pnd.48 M and .pnd.129 M.

L7 ANSWER 4 OF 10 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

2001214623 EMBASE **Treatment** options for patients with severe **rheumatoid arthritis** are gradually increasing. Drugs and Therapy Perspectives 17/12 (4-8) 18 Jun 2001.
Refs: 16.
ISSN: 1172-0360. CODEN: DTHPEE. Pub. Country: New Zealand. Language: English. Summary Language: English.

AB **Rheumatoid arthritis** is a chronic **inflammatory autoimmune disease** which affects approximately 0.5 to 1% of the population. Inflammation of synovial tissue in peripheral joints leads to joint erosion and eventual destruction resulting in significant pain, fatigue, functional disability and early mortality in affected patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as initial **treatment** but they offer symptomatic relief only and most patients require alternative or additional therapy. Disease modifying antirheumatic drugs (DMARDs) are now being given earlier in the course of the disease with the aim of reducing joint damage. However, few are fully effective when administered as monotherapy. Although the efficacy/toxicity

ratio of some of the older DMARDs (e.g. methotrexate, sulfasalazine) is favourable, their tolerability is not ideal and frequent monitoring for adverse events is required. Two agents which inhibit the production of the cytokines have recently been introduced. Infliximab and etanercept both inhibit tumour necrosis factor-.alpha. (TNF.alpha.) and have shown promising reductions in disease activity either alone or in combination with methotrexate. For patients unresponsive to monotherapy, combination regimens of DMARDs may improve responses.

L7 ANSWER 5 OF 10 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2000255501 EMBASE Management of the patient with severe refractory **rheumatoid arthritis**: Are the newer **treatment** options worth considering?. Lacki J.K., Dr. J.K. Lacki, Dept. of Rheumatol./Clinic. Immunol., Karol Marcinkowski University, School of Medical Sciences, Winogrady 144, 61-636 Poznan, Poland. lacki@post.pl.
BioDrugs 13/6 (425-439) 2000.
Refs: 136.
ISSN: 1173-8804. CODEN: BIDREP4. Pub. Country: New Zealand. Language: English. Summary Language: English.
AB **Rheumatoid arthritis** (RA) is a chronic, **inflammatory, autoimmune disease** leading to joint destruction. It is the most common cause of potentially treatable disabilities. The outcome of the disease varies from very mild to a refractory, rapidly progressive type with a high mortality rate. In recent years, profound changes in the traditional paradigms of RA therapy have been introduced. Instead of a therapeutically progressive approach, aggressive therapy is recommended for aggressive forms of RA. It has forced us to remodel the traditional **treatment** pyramid, and to start new strategies such as saw-tooth or step-down-bridge schedules. The last 10 years have seen wide acceptance of immunosuppressive therapy. These agents hold much promise for the further **treatment** of RA. A few years ago it seemed that we would be unable to influence the long term outcome in RA, but today the development of new drugs and techniques has increased our chances of fighting RA, and prospects for the future are even more promising.

L7 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2002 ACS
1999:783952 Document No. 132:18781 Use of cyclosporins in the **treatment** of **inflammatory autoimmune diseases**. Hiestand, Peter (Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.). PCT Int. Appl. WO 9962540 A1 19991209, 28 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-EP3770 19990531. PRIORITY: GB 1998-11854 19980602.
AB Non-immunosuppressive, cyclophilin-binding cyclosporins are useful in the **treatment** and prevention of **inflammatory autoimmune diseases**, such as **rheumatoid arthritis**. E.g., [MeIle]4-cyclosporin showed good inhibition of swelling of hind paw in the rat collagen-induced arthritis model at oral doses of 12.5 and 25 mg/kg twice daily up to approx. 60% of the effect of the proprietary COX inhibitor (used as control) at day 9 (dosed at 2.5 mg/kg twice daily, orally).

L7 ANSWER 7 OF 10 MEDLINE
1999236392 Document Number: 99236392. PubMed ID: 10219652. Oral tolerance in the **treatment** of **inflammatory autoimmune diseases**. Wardrop R M 3rd; Whitacre C C. (Ohio State University,

Department of Medical Microbiology and Immunology, Columbus 43210-1239, USA.) INFLAMMATION RESEARCH, (1999 Mar) 48 (3) 106-19. Ref: 154. Journal code: 9508160. ISSN: 1023-3830. Pub. country: Switzerland. Language: English.

AB Oral tolerance refers to the oral administration of protein antigens, which induces a state of systemic nonresponsiveness specific for the fed antigen. This method of inducing immune non-responsiveness has been applied to the prevention and **treatment** of experimental animal models of autoimmune disease. Extensive research in this area over the past ten years has led to the conclusion that two mechanisms are operative in the mediation of oral tolerance--active suppression and clonal anergy/deletion. A number of factors have been identified that determine which mechanism of tolerance is operative--antigen dose, antigen form, and the timing of antigen administration. Work from these animal models has recently been extended into human clinical trials of multiple sclerosis, **rheumatoid arthritis**, diabetes, uveitis, and allergy, with differing degrees of success. In this review, a discussion is provided of the animal model systems where oral tolerance has been applied and the clinical trials where an oral tolerization approach has been attempted. Moreover, recent mechanistic studies are reviewed and a model proposed for the induction of oral tolerance.

L7 ANSWER 8 OF 10 MEDLINE

89372468 Document Number: 89372468. PubMed ID: 2672925. Amiprilose hydrochloride for **rheumatoid arthritis**. Riskin W G; Gillings D B; Scarlett J A. (University of Miami School of Medicine, Florida.) ANNALS OF INTERNAL MEDICINE, (1989 Sep 15) 111 (6) 455-65. Journal code: 0372351. ISSN: 0003-4819. Pub. country: United States. Language: English.

AB STUDY OBJECTIVE: To assess the safety and efficacy of amiprilose hydrochloride (HCl), a novel synthetic carbohydrate with anti-inflammatory and immunomodulatory properties, in patients with **rheumatoid arthritis**. DESIGN: Prospective, multicenter, randomized, parallel group, double-blind placebo-controlled 12-week trial. PATIENTS: Two hundred and one functional class I and II patients with definite or classic **rheumatoid arthritis**, previously untreated with disease modifying antirheumatic drugs. INTERVENTIONS: Patients were withdrawn from nonsteroidal anti-inflammatory drug therapy. Those who flared were randomly assigned to amiprilose HCl, 6 g/d, or placebo for 12 weeks. No concomitant anti-inflammatory or antirheumatic drug therapy was permitted during the study. Combination acetaminophen and propoxyphene napsylate was the only supplemental analgesic medication allowed. MEASUREMENTS AND MAIN RESULTS: The number of painful joints and swollen joints, joint pain and joint swelling indices, left and right grip strength, investigator global assessment, and patient global assessment returned to baseline for the amiprilose group and showed statistically significant (P less than 0.05) differences from the placebo group within 4 to 6 weeks. The protocol criteria for overall therapeutic response were satisfied by 41% of the amiprilose patients, compared with 21% of the placebo group (P = 0.003). Approximately 0.5 tablet per day less analgesic medication was taken by the amiprilose group (P less than 0.05 at weeks 6 and 12). There were no statistically significant differences in morning stiffness, walking time, erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor between the groups. A similar number of adverse experiences were reported by the patients on amiprilose (67%) and on placebo (63%). One patient on amiprilose developed thrombocytopenia of unknown cause; no other reported adverse effects were serious. CONCLUSIONS: Amiprilose HCl has significant anti-inflammatory activity and a favorable safety profile when used as the sole antirheumatic therapy in patients with active **rheumatoid arthritis**. Synthetic carbohydrates may represent an important new class of drugs for the **treatment** of **inflammatory, autoimmune diseases**.

L7 ANSWER 9 OF 10 MEDLINE
89389509 Document Number: 89389509. PubMed ID: 2675492. [Initial clinical experiences in the **treatment** of chronic polyarthritis with a new monokine release inhibitor]. Erste klinische Erfahrungen in der Behandlung chronischer Polyarthritiden mit einem neuen Monokin-Release-Inhibitor. Seibel M J; Bruckle W; Respondek M; Beveridge T; Schnyder J; Muller W. (Orthopedic Research Laboratory, Columbia University Medical Center, New York.) ZEITSCHRIFT FUR RHEUMATOLOGIE, (1989 May-Jun) 48 (3) 147-51. Journal code: 0414162. ISSN: 0340-1855. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: German.

AB Cytokines such as Interleukin-1 (IL-1) are important modulators of the cell-mediated immune response and play a paramount role in **inflammatory autoimmune disease**. We report on preliminary clinical experiences with a new, tricyclic substance [(10-Methoxy-4H-benzo[4,5]cyclo-hepta-[1,2-b]thiophene-4- ylidene]acetic acid, MW 284), which inhibits the release of interleukin-1 alpha and -beta from cultured murine macrophages or human mononuclear cells. The study included 12 patients (**rheumatoid arthritis**, n = 9; hemochromatotic arthropathy, n = 1; psoriatic arthropathy, n = 1; seronegative spondylarthropathy, n = 1). Eight patients were treated for a total of 8 weeks, receiving a median dose of 800 mg/d of the substance. Due to significant clinical benefits, two patients continued for a total of six months. Administration of the drug was discontinued in two patients because of severe urticaria and lack of compliance, respectively. Four out of 10 patients showed clinical improvement according to Ritchie-Index, pain score, ESR and CRP. Side effects were diffuse gastrointestinal symptoms (4/12), temporary impairment of liver function (4/12) and allergic skin reactions (3/12).

L7 ANSWER 10 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
86196153 EMBASE Document No.: 1986196153. Methotrexate therapy in **rheumatoid arthritis**. Current status. Wilke W.S.; Mackenzie A.H.. Department of Rheumatic and Immunologic Disease, Cleveland Clinic Foundation, Cleveland, OH 44106, United States. Drugs 32/2 (103-113) 1986.
CODEN: DRUGAY. Pub. Country: Australia. Language: English.

AB Antimetabolites which inhibit the enzyme dihydrofolate reductase, including aminopterin and methotrexate (amethopterin) have been used in cancer and leukaemia chemotherapy since 1947. More recently, it has become a valuable alternative **treatment** for non-neoplastic diseases and has enjoyed its widest application in this respect as a **treatment** for severe psoriasis. In the subset of patients with psoriasis who develop erosive arthritis, early investigators observed improvement in both the skin and joint manifestations of psoriasis. Based largely on these observations, methotrexate has since been used to treat a variety of other arthritides and **inflammatory/autoimmune diseases** including Reiter's syndrome, polymyositis, polyarteritis nodosa, Wegener's granulomatosis, cyclitis, sarcoidosis and **rheumatoid arthritis**. In this article the authors discuss its use in **rheumatoid arthritis**.

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L4            117 S L3 AND INFLAMMATORY AUTOIMMUNE DISEASE
L5             41 DUP REMOVE L4 (76 DUPLICATES REMOVED)
L6             10 S L5 AND RHEUMATOID ARTHRITIS
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L10             1 "RSFTLASSETGVG"

=> d l10 cbib abs

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
1998:457273 Document No. 129:198014 Monoclonal antibody to cell surface
     antigens of autoimmune disease for therapeutical use and its preparation.
     Steenbakkers, Petrus Gerardus Antonius (AKZO N. V., Neth.). Jpn. Kokai
     Tokkyo Koho JP 10179160 A2 19980707 Heisei, 57 pp. (Japanese). CODEN:
     JKXXAF. APPLICATION: JP 1997-363807 19971127. PRIORITY: EP 1996-203465
     19961206; EP 1997-201972 19970627.
AB   Disclosed are a method for the prepn. of monoclonal antibody to a
     hard-to-obtain cell surface antigen by immunizing a mammalian animal with
     the purified antigen along with intact cells without using adjuvant,
     enriching the antigen-specific B cell population, and fusion of the
     immunized B cells with myeloma cells to obtain hybridoma cells secreting
     the monoclonal antibody. Prepn. of monoclonal antibody to T cell
     receptors (TCR) prepd. from a patient with autoimmune disease such as
     rheumatic disease was described, which comprises (1) immunization of
     BALB/C mice with 10^6 intact T cells of clone H.243 (with TCR of V.alpha.8+
     and V.beta.9+) and the purified TCR/CD3 complex (5x10^7 cells equiv.) and
     (2) fusion of the immunized B cells with NS-1 myeloma cells to obtain
     hybridoma clones TCR64, TCR66, TCR69, TCR70, TCR73, and TCR76. The
     monoclonal antibody recognizes epitope RSFTLASSETGVG from human
     cartilage gp-39 (HC gp-39).


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                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -1.86      -1.86

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FULL ESTIMATED COST                                   46.75      46.96

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L11          405 (BOOTS A?/AU OR MILTENBURG A?/AU)

=> s l11 and rheumatoid arthritis
L12          214 L11 AND RHEUMATOID ARTHRITIS

=> s l12 and HC gp39
L13            1 L12 AND HC GP39

=> d l13 cbib abs

L13  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1998:785564   Document No. 130:57290  Proteins and novel peptides derived from
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autoantigen for use in immunotherapy of autoimmune diseases. **Boots, Anna Maria Helena**; Verheijden, Gijsbertus Franciscus Maria; Bos, Ebo Sybren (Akzo Nobel N.V., Neth.). U.S. US 5843449 A 19981201, 19 pp., Cont.-in-part of U.S. 5,736,507. (English). CODEN: USXXAM. APPLICATION: US 1996-634493 19960418. PRIORITY: US 1996-613645 19960325.

AB The present invention relates to novel peptides derived from the autoantigen HC gp-39, said peptides comprising at least one of the amino acid sequences PGRSFTILAS (SEQ ID No. 1), FTLASSETG (SEQ ID No. 2), YDDQESVKS (SEQ ID No. 3) and FSKIASNTQ (SEQ ID No. 4). The peptides resemble MHC Class II restricted T-cell epitopes present on the autoantigen HC gp-39 in articular cartilage. HC gp-39, proteins comprising an amino acid sequence which exhibits at least 50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFANISND (SEQ ID No: 10) and said peptides can be used in antigen-specific treatment of articular cartilage destruction in autoimmune diseases in mammals to induce systemic tolerance of the immune system. The autoantigen HC gp-39, proteins comprising an amino acid sequence which exhibits at least 50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFA NISND (SEQ ID NO: 10) and said peptides are also suitable to induce arthritis in animals, preferably mice. The invention furthermore relates to pharmaceutical comps. comprising said autoantigen and/or said peptides, a diagnostic method for the detection of autoreactive T cells in a test sample and test kits to be used in said method. For treating T cell-mediated cartilage destruction disease (e.g. arthritis or **rheumatoid arthritis**), the T cell-specific tolerance-inducing peptide or protein can also be selected from the group consisting of pig heparin binding 38 kDa protein, bovine 39 kDa whey protein, murine breast regressing 39 kDa protein (brp39), human oviduct-specific glycoprotein, murine oviduct-specific glycoprotein, hamster oviduct-specific glycoprotein, bovine oviduct-specific glycoprotein, human chitotriosidase precursor and their fragments.

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=> d his

     (FILE 'HOME' ENTERED AT 13:01:49 ON 26 AUG 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 13:01:58 ON
     26 AUG 2002
L1             0 S "HC GP-39"
L2             0 S "HC GP39"
L3       6863469 S TREATMENT
L4           117 S L3 AND INFLAMMATORY AUTOIMMUNE DISEASE
L5            41 DUP REMOVE L4 (76 DUPLICATES REMOVED)
L6            10 S L5 AND RHEUMATOID ARTHRITIS
L7            10 DUP REMOVE L6 (0 DUPLICATES REMOVED)
L8             0 S L5 AND "PGRSFTLAS"
L9             0 S L5 AND "PSFTLASSETGVG"
L10            1 S "PSFTLASSETGVG"

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 13:16:59 ON
     26 AUG 2002
L11          405 S (BOOTS A?/AU OR MILTENBURG A?/AU)
L12          114 S L11 AND RHEUMATOID ARTHRITIS
L13            1 S L12 AND HC GP39

=> s l12 and collagen arthritis
L14            0 L12 AND COLLAGEN ARTHRITIS

=> dup remove l12
PROCESSING COMPLETED FOR L12
L15           85 DUP REMOVE L12 (129 DUPLICATES REMOVED)
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=> s l15 and "HC gp-39"
L16 16 L15 AND "HC GP-39"

=> dup remove l16
PROCESSING COMPLETED FOR L16
L17 16 DUP REMOVE L16 (0 DUPLICATES REMOVED)

=> d l17 1-16 cbib abs

L17 ANSWER 1 OF 16 MEDLINE
2002195319 Document Number: 21963556. PubMed ID: 11874932. Long term anti-tumour necrosis factor alpha monotherapy in **rheumatoid arthritis**: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. den Broeder A A; Joosten L A B; Saxne T; Heinegard D; Fenner H; **Miltenburg A M M**; Frasa W L H; van Tits L J; Buurman W A; van Riel P L C M; van de Putte L B A; Barrera P. (Department of Rheumatology, University Medical Centre Nijmegen, The Netherlands.. A.denbroeder@aig.azn.nl) . ANNALS OF THE RHEUMATIC DISEASES, (2002 Apr) 61 (4) 311-8. Journal code: 0372355. ISSN: 0003-4967. Pub. country: England: United Kingdom. Language: English.
AB OBJECTIVES: To investigate the effect of prolonged neutralisation of tumour necrosis factor alpha (TNFalpha) on the radiological course in **rheumatoid arthritis** (RA). To assess whether the radiological course can be predicted by clinical variables or biological markers of cartilage and synovium turnover and of endothelial activation. PATIENTS AND METHODS: Forty seven patients with active RA enrolled at our centre in monotherapy trials with adalimumab (D2E7), a fully human anti-TNFalpha monoclonal antibody, were studied for two years. Radiographs of hands and feet obtained at baseline and after one and two years were scored in chronological order by a single, blinded observer using the modified Sharp method. Radiological course was classified as stable or progressive using the smallest detectable difference as cut off point. The relation between radiological course and serum markers of cartilage and synovium turnover (metalloproteinases (MMP-1 and MMP-3), cartilage oligomeric matrix protein (COMP), human cartilage glycoprotein-39 (**HC gp-39**), endothelial activation (soluble E-selectin and intercellular adhesion molecule (ICAM-1)), and integrated measures of disease activity were assessed using univariate and multivariate analysis. RESULTS: Radiological evaluation was performed in 36 patients with paired sets of radiographs at baseline and two years. After two years a total of 15/36 (42%) presented no radiological progression. More patients with stable radiological course were still receiving anti-TNFalpha treatment after two years (13/15 (87%) v 11/21 (52%); p=0.03) and had lower baseline COMP and sICAM-1 levels (p=0.01 and 0.04, respectively) than those in the group with progressive disease. In a logistic regression model the combination of sustained TNF neutralisation and baseline COMP and sICAM-1 levels was predictive for radiological outcome (p=0.03). C reactive protein and disease activity score area under the curve were significantly correlated with changes in radiological scores after two years (r=0.48 and 0.37, p<0.05). Long term TNFalpha neutralisation decreased the levels of COMP, sICAM, MMPs, and **HC gp-39**, but not sE-selectin. CONCLUSION: The results suggest that long term monotherapy with anti-TNFalpha has a positive effect on radiological outcome and modulates cartilage and synovium turnover as measured by biological markers. Baseline serum sICAM-1 levels and COMP levels may be helpful to identify patients with progressive or non-progressive radiological outcome.

L17 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2002 ACS
2001:360756 Document No. 134:320857 Modified peptides and peptidomimetics for use in immunotherapy. Van Staveren, Catherina Joanna; Timmers, Cornelis Marius; Van Galen, Philippus Johannes Marie; Knegtel, Ronaldus Marcellus Alphonsus; **Boots, Anna Maria Helena; Miltenburg,**

Andreas Martinus Maria (Akzo Nobel N.V., Neth.). PCT Int. Appl. WO 2001029081 A1 20010426, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP10230 20001018. PRIORITY: EP 1999-203427 19991018.

AB The invention relates to a modified peptide derived from formula I peptide H-Arg-Ser-Phe-Thr-Leu-Ala-Ser-Ser-Glu-Thr-Gly-Val-Gly-OH (peptide (263-275) of cartilage-derived protein human cartilage gp-39 (**HC gp-39**)) having general formula (II): Q-A1-A2-A3-A4-A5-A6-A7-A8-A9-A10-A11-A12-A13-Z. In general formula (II), A1 through A13 correspond with the amino acids of formula (I), Q corresponds with H and Z corresponds with OH. The modifications according to the present invention are selected from one or more of the groups a, b or c, consisting of (a) substitution of 1-6, preferably 1-4 amino acids at A1 through A13 with non-natural amino acids or .beta. amino acids; (b) substitution of one or more amide bonds with reduced amide bonds or ethylene isosteres; (c) substitutions at Q and/or Z and, optionally, (d) substitution of natural amino acids up to a total of 6 modifications. The peptides can be used for inducing tolerance induction in patients suffering from autoimmune diseases. The most potent compds. were Ac-Arg-Ser-Phe-Thr-Leu-Ala-Ser-Ser-Glu-Thr-Gly-Val-Gly-OH, Ac-Arg-Ser-Phe-Thr-Leu-Ala-Ser-Ser-Glu-Thr-Gly-Val-.psi.[CH2NH]-Gly-NH2, Ac-Arg-NhSer-Phe-Thr-Leu-Ala-Ser-Ser-Glu-Thr-Gly-Val-Gly-NH2 and Ac-Arg-NhSer-Phe-Thr-Leu-Ala-Ser-Ser-Glu-Thr-Gly-Val-.psi.[CH2NH]-Gly-NH2.

L17 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2002 ACS

2000:84638 Document No. 132:121462 Use of human cartilage (**HC**) **gp-39** in immune diseases. **Miltenburg, Andreas Martinus Maria; Boots, Anna Maria Helena** (Akzo Nobel N.V., Neth.). PCT Int. Appl. WO 2000004917 A2 20000203, 29 pp. DESIGNATED STATES: W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-EP5131 19990719. PRIORITY: EP 1998-202471 19980723.

AB The present invention relates to the use of **HC gp-39** to prevent (auto)immune disease or inflammatory diseases, e.g. **rheumatoid arthritis**. More specifically, **HC gp-39** or fragments thereof can be used to modulate the reactivity of lymphocytes which are reactive to antigens other than **HC gp-39** but which are present in the same tissue as where **HC gp-39** is being expressed.

L17 ANSWER 4 OF 16 MEDLINE

2001101205 Document Number: 20579841. PubMed ID: 11136874. Cellular immune response to human cartilage glycoprotein-39 (**HC gp-39**)-derived peptides in **rheumatoid arthritis** and other inflammatory conditions. Vos K; **Miltenburg A M**; van Meijgaarden K E; van den Heuvel M; Elferink D G; van Galen P J; van Holzeband R A; van Vliet-Daskalopoulou E; Ottenhoff T H; Breedveld F C; **Boots A M**; de Vries R R. (Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands.) RHEUMATOLOGY, (2000 Dec) 39 (12) 1326 31. Journal code: 100883501. ISSN: 1462-0324. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To study the specificity of the peripheral blood mononuclear cell (PBMC) response to peptides derived from human cartilage glycoprotein-39 (**HC gp-39**) in patients with

rheumatoid arthritis (RA) and the correlation between this response and disease activity. METHODS: RA patients, patients with systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) or osteoarthritis (OA) and healthy controls were studied. All individuals were typed for HLA-DRB1 and their disease activity score was documented. Proliferation of PBMC was measured following incubation with five different **HC gp-39**-derived peptides, selected by the use of a DR4 (DRB1*0401) binding motif. RESULTS: A proliferative response to one of the five peptides (peptide 259-271 at 10 microg/ml) was more often observed in RA patients than in healthy controls (P=0.001). RA patients who expressed DRB1*0401 more often showed a response against this peptide than RA patients who did not express this RA-associated haplotype. This response was not RA-specific since patients with IBD or OA also showed a response significantly more frequently than healthy controls (P:=0.02 and P=0.03 respectively). However, the level of the response against peptide 259-271 correlated with disease activity in RA patients but not in patients with IBD or SLE. Increased responses to **HC gp-39** 263-275 were found in patients with IBD or OA; a trend towards such a response failed to reach significance in RA patients in this study. CONCLUSION: In RA patients as well as in patients with other inflammatory conditions, **HC gp-39**-derived peptides may be targets of the T-cell-mediated immune response. In the RA patient group the immune response to **HC gp-39**-derived peptide 259-271 correlated with disease activity.

L17 ANSWER 9 OF 16 MEDLINE

2000313929 Document Number: 20313929. PubMed ID: 10857782. Human cartilage gp-39+,CD16+ monocytes in peripheral blood and synovium: correlation with joint destruction in **rheumatoid arthritis**. Baeten D; **Boots A M**; Steenbakkers P G; Elewaut D; Bos E; Verheijden G F; Berheijden G; **Miltenburg A M**; Rijnders A W; Veys E M; De Keyser F. (Department of Rheumatology, Ghent University Hospital, Belgium.) ARTHRITIS AND RHEUMATISM, (2000 Jun) 43 (6) 1233-43. Journal code: 0370605. ISSN: 0004-3591. Pub. country: United States. Language: English.

AB OBJECTIVE: To investigate the expression of human cartilage (**HC**) **gp-39**, a possible autoantigen in **rheumatoid arthritis** (RA), in peripheral blood and synovium, to characterize its cellular source, and to analyze correlations with clinical features. METHODS: The expression of **HC gp-39** in synovium and peripheral blood mononuclear cells (PBMC) was assessed by immunohistochemistry and flow cytometry. Synthesis and secretion were investigated by both reverse transcription-polymerase chain reaction and enzyme-linked immunosorbent assay. RESULTS: PBMC expressing **HC gp-39** were increased in RA patients compared with spondylarthropathy patients (P = 0.0029) and with healthy control subjects (P = 0.0013). **HC gp-39**+ cells were also slightly overrepresented in RA synovium (P = 0.01). In both blood and synovium, **HC gp-39**+ cells were identified as CD14dim,CD16+ monocytes, a phenotype which can differentiate from classic CD14++ monocytes by maturation in vitro. **HC gp-39** messenger RNA was detected in RA synovium and PBMC, and PBMC secreted **HC gp-39** in vitro. The number of **HC gp-39**+ PBMC correlated with serum levels of C-reactive protein (r = 0.88, P = 0.008) and **HC gp-39** (r = 0.92, P = 0.014). **HC gp-39** expression in RA synovial lining correlated with joint destruction (r = 0.77, P < 0.001). CONCLUSION: CD16+ monocytes, a cellular source of **HC gp-39** in vivo, are overrepresented in both RA peripheral blood and synovial tissue. The presence of **HC gp-39**+ cells in RA synovium is correlated with the degree of joint destruction. These data support a role of these cells in

the local autoimmune response that leads to chronic inflammation and joint destruction.

L17 ANSWER 6 OF 16 MEDLINE
2000191103 Document Number: 20191103. PubMed ID: 10728759. Induction of tolerance with intranasal administration of human cartilage gp-39 in DBA/1 mice: amelioration of clinical, histologic, and radiologic signs of type II collagen-induced arthritis. Joosten L A; Coenen-de Roo C J; Helsen M M; Lubberts E; **Boots A M**; van den Berg W B; **Miltenburg A M**. (Department of Rheumatology, University Hospital Nijmegen, The Netherlands.) ARTHRITIS AND RHEUMATISM, (2000 Mar) 43 (3) 645-55. Journal code: 0370605. ISSN: 0004-3591. Pub. country: United States. Language: English.

AB OBJECTIVE: Human cartilage glycoprotein 39 (**HC gp-39**) was recently identified as a candidate autoantigen in the pathogenesis of **rheumatoid arthritis**. In the present studies, we investigated the capacity of **HC gp-39** to interfere in clinical disease induced by an unrelated autoantigen, type II collagen (CII), by the induction of cross-tolerance. METHODS: DBA-1j/Bom mice were immunized with bovine CII/complete Freund's adjuvant and were given intraperitoneal booster injections of CII on day 21. Tolerance was induced via the intranasal pathway with either the disease-inducing antigen (CII), a control antigen (ovalbumin), or **HC gp-39** either before priming with CII or near the day of the booster injection. Arthritis was monitored visually, and joint pathology was examined histologically and radiologically. In addition, CII antibody levels in serum were analyzed by enzyme-linked immunosorbent assay. RESULTS: In contrast to treatment before priming, intranasal application of **HC gp-39** after immunization markedly suppressed disease activity and prevented joint destruction, whereas application of ovalbumin or CII was ineffective. Interference of **HC gp-39** with the immune response to CII was demonstrated by decreased anti-CII antibody levels. The combined data indicate that intranasal treatment with **HC gp-39** may trigger modulatory or regulatory mechanisms that interfere with the expression of disease in murine collagen-induced arthritis. CONCLUSION: **HC gp-39** is the first cross-tolerance-inducing protein in arthritis that down-modulates a spectrum of disease features when given in a semitherapeutic protocol.

L17 ANSWER 7 OF 16 MEDLINE
2000400313 Document Number: 20334013. PubMed ID: 10873965. Raised human cartilage glycoprotein-39 plasma levels in patients with **rheumatoid arthritis** and other inflammatory conditions. Vos K; Steenbakkers P; **Miltenburg A M**; Bos E; van Den Heuvel M W; van Hogezand R A; de Vries R R; Breedveld F C; **Boots A M**. (Department of Rheumatology, LUMC, Leiden, The Netherlands.. kvos@rheumatology.azl.nl) . ANNALS OF THE RHEUMATIC DISEASES, (2000 Jul) 59 (7) 544-8. Journal code: 0372355. ISSN: 0003-4967. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To evaluate plasma human cartilage glycoprotein (**HC gp-39**) as a possible marker for the presence and/or activity of **rheumatoid arthritis** (RA) and other inflammatory conditions. BACKGROUND: **HC gp-39** is a secretory product of chondrocytes, synovial cells, macrophages, and neutrophils. **HC gp-39**, also described as YKL-40, was found to be a marker of joint disease and tissue injury in RA and various other diseases. METHODS: Levels of **HC gp-39** were determined by a sandwich enzyme linked immunosorbent assay (ELISA) in 47 patients with RA, 47 with osteoarthritis (OA), 24 with systemic lupus erythematosus (SLE), 24 with inflammatory bowel disease (IBD), and in 47 healthy controls. A disease activity score was assessed in the patients with RA, SLE, and IBD. RESULTS: The plasma level of

HC gp-39 in the RA patient group was significantly higher than in the other patient groups and healthy controls. The level in patients with OA, SLE, and IBD was also significantly higher than the **HC gp-39** level found in the healthy control group. **HC gp-39** levels in patients with RA correlated positively with the ESR and IgM rheumatoid factor level but not with other variables of disease activity. In the patients with SLE and IBD no correlation was found with the disease activity score. CONCLUSION: The plasma level of **HC gp-39** is increased in inflammatory conditions with and without joint disease (SLE, IBD, OA, and RA). Thus increased levels of **HC gp-39** do not only reflect joint disease but also reflect inflammation or tissue degradation in various conditions. Notably, the highest level of **HC gp-39** was found in patients with RA. Only in the RA patient group was a correlation between **HC gp-39** plasma levels and some laboratory variables of disease activity found.

L17 ANSWER 8 OF 16 SCISEARCH COPYRIGHT 2002 ISI (R)
1999:899819 The Genuine Article (R) Number: 242JG. **HC gp-39** expression by CD16+'mature' monocytes: Relation with erosivity of **rheumatoid arthritis**.. Baeten D (Reprint); **Boots A M H**; Steenbakkers P; Verheijden G F M; **Miltenburg A M M**; Rijnders A W M; Verbruggen G; Veys E M; DeKeyser F. ARTHRITIS AND RHEUMATISM (SEP 1999) Vol. 42, No. 9, Supp. [S], pp. 1040-1040. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106. ISSN: 0004-3591. Language: English.

L17 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:528523 Document No.: PREV199900528523. **HC gp-39** expression by CD16+ mature monocytes: Relation with erosivity of **rheumatoid arthritis**. Baeten, D. (1); **Boots, A. M. H.**; Steenbakkers, P.; Verheijden, G. F. M.; **Miltenburg, A. M. M.**; Rijnders, A. W. M.; Verbruggen, G.; Veys, E. M.; De Keyser, F.. (1) Ghent Belgium. Arthritis & Rheumatism, (Sept., 1999) Vol. 42, No. 9 SUPPL., pp. S244. Meeting Info.: 63rd Annual Scientific Meeting of the American College of Rheumatology and the 34th Annual Scientific Meeting of the Association of Rheumatology Health Professionals Boston, Massachusetts, USA November 13-17, 1999 ISSN: 0004-3591. Language: English.

L17 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2002 ACS
2000:243123 Document No. 133:250925 Human cartilage gp-39 as candidate autoantigen for immunotherapy of **rheumatoid arthritis**. **Boots, Annemieke M. H.**; Verheijden, Gijs F.; Roo, Christina J. J. Coenen-De; **Miltenburg, Andre M. M.**; Hubers, Henk; Cope, Andrew P.; Sonderstrup-McDevitt, Grete; Rijnders, Antonius W. M. (Departments of Pharmacology and Target discovery, NV Organon, Oss, Neth.). Verhandelingen - Koninklijke Nederlandse Akademie van Wetenschappen, Afdeling Natuurkunde, Tweede Reeks, 101(Specific Immunotherapy of Chronic Autoimmune Diseases), 93-96 (English) 1999. CODEN: VNAWAG. ISSN: 0373-465X. Publisher: Royal Netherlands Academy of Arts and Sciences.
AB A review with 12 refs. The cartilage-derived antigen, human cartilage glycoprotein-39 may be a relevant autoantigen for immunotherapy of **rheumatoid arthritis** (RA). A study was conducted and showed that there is a higher frequency of **HC gp-39** reactive T cells in DRB1*0401 peptide-pos. RA patients when compared to DRB1*0401-matched healthy controls. Also, preliminary data indicated that the presence of **HC gp-39** in DRB1*0401-pos. individuals is assocd. with the prodn. of proinflammatory mediators, thereby suggesting that **HC gp-39** recognition may be involved in perpetuation of the chronic inflammatory process as seen in RA. Thus, **HC gp-39** is a

prime candidate for antigen-specific immunotherapy of PA.

L17 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2002 ACS
1998:785564 Document No. 130:37290 Proteins and novel peptides derived from autoantigen for use in immunotherapy of autoimmune diseases. **Boots, Anna Maria Helena**; Verheijden, Gijsbertus Franciscus Maria; Bos, Ebo Sybren (Akzo Nobel N.V., Neth.). U.S. US 5843449 A 19981201, 19 pp., Cont.-in-part of U.S. 5,736,507. (English). CODEN: USXXAM. APPLICATION: US 1996-634493 19960418. PRIORITY: US 1996-619645 19960325.
AB The present invention relates to novel peptides derived from the autoantigen **HC gp-39**, said peptides comprising at least one of the amino acid sequences FGRSFTILAS (SEQ ID No. 1), FTLASSETG (SEQ ID No. 2), YDDQESVKS (SEQ ID No. 3) and FSKIASNTQ (SEQ ID No. 4). The peptides resemble MHC class II restricted T-cell epitopes present on the autoantigen **HC gp-39** in articular cartilage. **HC gp-39**, proteins comprising an amino acid sequence which exhibits at least 50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFANISND (SEQ ID No: 10) and said peptides can be used in antigen-specific treatment of articular cartilage destruction in autoimmune diseases in mammals to induce systemic tolerance of the immune system. The autoantigen **HC gp-39**, proteins comprising an amino acid sequence which exhibits at least 50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFANISND (SEQ ID NO: 10) and said peptides are also suitable to induce arthritis in animals, preferably mice. The invention furthermore relates to pharmaceutical compns. comprising said autoantigen and/or said peptides, a diagnostic method for the detection of autoreactive T cells in a test sample and test kits to be used in said method. For treating T cell-mediated cartilage destruction disease (e.g. arthritis or **rheumatoid arthritis**), the T cell-specific tolerance-inducing peptide or protein can also be selected from the group consisting of pig heparin binding 38 kDa protein, bovine 39 kDa whey protein, murine breast regressing 39 kDa protein (brp39), human oviduct-specific glycoprotein, murine oviduct-specific glycoprotein, hamster oviduct-specific glycoprotein, bovine oviduct-specific glycoprotein, human chitotriosidase precursor and their fragments.

L17 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1998:470378 Document No.: PREV199800470378. **HC gp-39** expression in synovial lining is correlated with joint destruction in RA. Baeten, D. (1); Dekeyser, F. (1); Elewaut, D. (1); Fijnders, A. M. W.; Verheijden, G. F.; **Miltenburg, A. M. W.**; Steenbakkers, P.; Verbruggen, G. (1); **Boots, A. M. H.**; Veys, E. M. (1). (1) Dep. Rheumatol., Univ. Hosp. Ghent, Ghent, Belguim. Arthritis & Rheumatism, (Sept., 1998) Vol. 41, No. 9 SUPPL., pp. S365. Meeting Info.: 62nd National Scientific Meeting of the American College of Rheumatology and the 33rd National Scientific Meeting of the Association of Rheumatology Health Professionals San Diego, California, USA November 8-12, 1998 American College of Rheumatology. ISSN: 0004-3591. Language: English.

L17 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1998:470103 Document No.: PREV199800470103. **HC gp-39** is expressed by peripheral blood mononuclear cells in RA. Baeten, D. (1); De Keyser, F. (1); Steenbakkers, P.; Verheijden, G. G. (1); Bos, E. S. (1); Fijnders, A. M. W.; Verbruggen, G. (1); **Boots, A. M. H.**; Veys, E. M. (1). (1) Dep. Rheumatol., Univ. Hosp. Ghent, Ghent Belgium. Arthritis & Rheumatism, (Sept., 1998) Vol. 41, No. 9 SUPPL., pp. S320. Meeting Info.: 62nd National Scientific Meeting of the American College of Rheumatology and the 33rd National Scientific Meeting of the Association of Rheumatology Health Professionals San Diego, California, USA November 8-12, 1998 American College of Rheumatology. ISSN: 0004-3591. Language: English.

L17 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2002 ACS
1997:718004 Document No. 128:16403 Human cartilage autoantigen glycoprotein gp-39 and proteins structurally related thereto for use in immunotherapy of autoimmune diseases. **Boots, Anna Maria Helena**; Verheijden, Gijsbertus Franciscus Maria; Bos, Ebo Sybren (Akzo Nobel N.V., Neth.; Boots, Anna Maria Helena; Verheijden, Gijsbertus Franciscus Maria; Bos, Ebo Sybren). PCT Int. Appl. WO 9740149 A1 19971030, 38 pp. DESIGNATED STATES: W: AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-EP1903 19970415. PRIORITY: US 1996-634493 19960418.

AB The present invention relates to the use of autoantigen **HC gp-39** (human cartilage glycoprotein-39), and proteins comprising an amino acid sequence which exhibits .gtoreq.50% homol. with the amino acid sequence of **HC gp-39**, and more particular with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFL CTHIIYSFANISND in antigen-specific treatment of articular cartilage destruction in autoimmune diseases in mammals to induce systemic tolerance of the immune system. The autoantigen **HC gp-39**, and the arthritogenic proteins comprising an amino acid sequence which exhibits .gtoreq.50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFANISND are also suitable to induce arthritis in animals, preferably mice. The arthritogenicity and cloning of bovine 39-kDa whey protein is also described. The invention furthermore relates to pharmaceutical compns. comprising said autoantigen and/or said arthritogenic proteins, a diagnostic method for the detection of autoreactive T cells in a test sample and test kits to be used in said method.

L17 ANSWER 15 OF 16 MEDLINE
97325910 Document Number: 97325910. PubMed ID: 9182922. Human cartilage glycoprotein-39 as a candidate autoantigen in **rheumatoid arthritis**. Verheijden G F; Rijnders A W; Bos E; Coenen-de Roo C J; van Staveren C J; **Miltenburg A M**; Meijerink J H; Elewaut D; de Keyser F; Veys E; **Boots A M**. (NV Organon, Oss, The Netherlands.) ARTHRITIS AND RHEUMATISM, (1997 Jun) 40 (6) 1115-25. Journal code: 0370605. ISSN: 0004-3591. Pub. country: United States. Language: English.

AB OBJECTIVE: To identify a cartilage-derived autoantigen that is relevant to the **rheumatoid arthritis** (RA) disease process.
METHODS: A DR4 (DRB1*0401) peptide binding motif was used for the selection of potential self reactive peptides within human cartilage glycoprotein-39 (**HC gp-39**), a protein that is differentially expressed at the site of chronic inflammation. Synthetic peptides accommodating the motif were tested for binding the RA-associated DR4 (DRB1*0401) molecules. High-affinity binders were then tested for their capacity to stimulate peripheral blood mononuclear cell responses in RA patients or healthy donors. To assess the arthritogenic nature of native **HC gp-39**, the protein was injected into BALB/c mice. RESULTS: **HC gp-39**-derived motif-based peptides were selectively recognized by peripheral blood T cells from RA patients. Injection of the intact protein into BALB/c mice resulted in immunity to **HC gp-39**, which was found to be associated with the development of a chronic, relapsing arthritis. Moreover, inhalation of the protein led to tolerization of antigen-specific T cells and to suppression of **HC gp-39**-induced arthritis. CONCLUSION: These data indicate that **HC gp-39** is a target of the immune response in RA. Consequently, **HC gp-39** is a candidate for antigen-specific immunotherapy.

L17 ANSWER 16 OF 16 SCISEARCH COPYRIGHT 2002 ISI (R)
1998:153262 The Genuine Article (R) Number: YX351. Generation and functional characterization of anti-clonotype antibodies to human T-cell receptors. Steenbakkers P G A (Reprint ; **Boots A M H**; Rijnders A W M. NV ORGANON, DEPT IMMUNOL, POB 20, NL-5340 BH OSS, NETHERLANDS (Reprint). JOURNAL OF IMMUNOLOGICAL METHODS (15 DEC 1997) Vol. 210, No. 1, pp. 51-64. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS . ISSN: 0022-1759. Pub. country: NETHERLANDS. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Monoclonal antibodies (mAb) directed against the clonotypic structure of the T-cell receptor (TCR) may be useful reagents in the study and therapy of T-cell-mediated diseases. In contrast to several reports concerning the generation of anti-clonotype mAb to mouse TCR, only very limited numbers of anti-clonotype mAb to human TCR have been described. So far, a suitable method for the generation of anti-clonotype mAb to a given TCR has not been available and in this report we describe a novel strategy for the generation of such mAb. Mice were immunized with intact human T-cells. Then, spleen cell populations were precleared from B-cells reactive to CD3 and the constant region of the TCR by adsorption to TCR/CD3 complexes derived from an irrelevant T-cell clone. Subsequently, clonotype-specific B-cells were selected with TCR/CD3 complexes from the T-cell clone of interest. The small number of B-cells resulting from this selection were clonally expanded in a B-cell culture system and then immortalized by mini-electrofusion. Ten clonotype-specific mAb were generated against a DRB1 *0401-restricted T-cell clone recognizing an epitope of the human cartilage glycoprotein 39 (**HC gp-39**) All mAb immunoprecipitated a heterodimeric 85 kDa protein. Absolute specificity was demonstrated in a T-cell agglutination test with the T-cell clone of interest compared to a set of 16 defined, irrelevant T-cell clones or lines. In functional assays, the mAb were found to inhibit or block antigen-specific T-cell stimulation. In addition, crosslinked mAb were found to stimulate proliferation of the specific clone in the absence of antigen and antigen presenting cells (APC). Such mAb may have clinical relevance in deleting or modulating autoreactive T-cells in a clonotype-specific manner. (C) 1997 Elsevier Science B.V.

=> d his

(FILE 'HOME' ENTERED AT 13:01:45 ON 26 AUG 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 13:01:58 ON 26 AUG 2002

L1 0 S "HC GP-39"
L2 0 S "HC GP39"
L3 6863488 S TREATMENT
L4 117 S L3 AND INFLAMMATORY AUTOIMMUNE DISEASE
L5 41 DUP REMOVE L4 (76 DUPLICATES REMOVED)
L6 10 S L5 AND RHEUMATOID ARTHRITIS
L7 10 DUP REMOVE L6 (0 DUPLICATES REMOVED)
L8 0 S L5 AND "FGFSFTLAS"
L9 0 S L5 AND "RSFTLASSETGVG"
L10 1 S "RSFTLASSETGVG"

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 13:16:59 ON 26 AUG 2002

L11 405 S (BOOTS A?/AU OR MILTENBURG A?/AU)
L12 214 S L11 AND RHEUMATOID ARTHRITIS
L13 1 S L11 AND HC GP39
L14 0 S L12 AND COLLAGEN ARTHRITIS
L15 85 DUP REMOVE L12 (129 DUPLICATES REMOVED)
L16 16 S L15 AND "HC GP-39"
L17 16 DUP REMOVE L16 (0 DUPLICATES REMOVED)

```
=> s l15 and "HC gp-39"
L18          16 L15 AND "HC GP-39"

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19          16 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> s l19 and "RSFTLASSETGVG"
L20           0 L19 AND "RSFTLASSETGVG"

=> s l12 and "FGRSFTLAS"
L21           0 L12 AND "FGRSFTLAS"

=> s l12 and "FTLASSETG"
L22           1 L12 AND "FTLASSETG"

=> d 122 cbib abs

L22  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1998:785564   Document No. 130:37290  Proteins and novel peptides derived from
     autoantigen for use in immunotherapy of autoimmune diseases.  Boots,
     Anna Maria Helena; Verheijden, Gijsbertus Franciscus Maria; Bos, Ebo
     Sybren (Akzo Nobel N.V., Neth.).  U.S. US 5843449 A  19981201, 19 pp.,
     Cont.-in-part of U.S. 5,736,507.  (English).  CODEN: USXXAM.  APPLICATION:
     US 1996-634493 19960418.  PRIORITY: US 1996-619645 19960325.
AB   The present invention relates to novel peptides derived from the
     autoantigen HC gp-39, said peptides comprising at least one of the amino
     acid sequences FGRSFTILAS (SEQ ID No. 1), FTLASSETG (SEQ ID No.
     2), YDDQESVKS (SEQ ID No. 3) and FSKIASNTQ (SEQ ID No. 4).  The peptides
     resemble MHC Class II restricted T-cell epitopes present on the
     autoantigen HC gp-39 in articular cartilage.  HC gp-39, proteins
     comprising an amino acid sequence which exhibits at least 50% homol. with
     the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFANISND (SEQ
     ID No: 10) and said peptides can be used in antigen-specific treatment of
     articular cartilage destruction in autoimmune diseases in mammals to
     induce systemic tolerance of the immune system.  The autoantigen HC gp-39,
     proteins comprising an amino acid sequence which exhibits at least 50%
     homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFA
     NISND (SEQ ID NO: 10) and said peptides are also suitable to induce
     arthritis in animals, preferably mice.  The invention furthermore relates
     to pharmaceutical comprns. comprising said autoantigen and/or said
     peptides, a diagnostic method for the detection of autoreactive T cells in
     a test sample and test kits to be used in said method.  For treating T
     cell-mediated cartilage destruction disease (e.g. arthritis or
     rheumatoid arthritis), the T cell-specific
     tolerance-inducing peptide or protein can also be selected from the group
     consisting of pig heparin binding 36 kDa protein, bovine 39 kDa whey
     protein, murine breast regressing 39 kDa protein (brp39), human
     oviduct-specific glycoprotein, murine oviduct-specific glycoprotein,
     hamster oviduct-specific glycoprotein, bovine oviduct-specific
     glycoprotein, human chitotriosidase precursor and their fragments.


=> s l12 and "YDDQESVKS"
L23           1 L12 AND "YDDQESVKS"

=> d 123 cbib abs

L23  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1998:785564   Document No. 130:37290  Proteins and novel peptides derived from
     autoantigen for use in immunotherapy of autoimmune diseases.  Boots,
     Anna Maria Helena; Verheijden, Gijsbertus Franciscus Maria; Bos, Ebo
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Sykren (Akzo Nobel N.V., Neth.). U.S. US 5843449 A 19981201, 19 pp., Cont.-in-part of U.S. 5,736,507. (English). CODEN: USXXAM. APPLICATION: US 1996-634493 19960418. PRIORITY: US 1996-619645 19960325.

AB The present invention relates to novel peptides derived from the autoantigen HC gp-39, said peptides comprising at least one of the amino acid sequences FGRSFTILAS (SEQ ID No. 1), FTLASSETG (SEQ ID No. 2), **YDDQESVKS** (SEQ ID No. 3) and FSKIASNTQ (SEQ ID No. 4). The peptides resemble MHC Class II restricted T-cell epitopes present on the autoantigen HC gp-39 in articular cartilage. HC gp-39, proteins comprising an amino acid sequence which exhibits at least 50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFANISND (SEQ ID No: 10) and said peptides can be used in antigen-specific treatment of articular cartilage destruction in autoimmune diseases in mammals to induce systemic tolerance of the immune system. The autoantigen HC gp-39, proteins comprising an amino acid sequence which exhibits at least 50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFA NISND (SEQ ID NO: 10) and said peptides are also suitable to induce arthritis in animals, preferably mice. The invention furthermore relates to pharmaceutical compns. comprising said autoantigen and/or said peptides, a diagnostic method for the detection of autoreactive T cells in a test sample and test kits to be used in said method. For treating T cell-mediated cartilage destruction disease (e.g. arthritis or **rheumatoid arthritis**), the T cell-specific tolerance-inducing peptide or protein can also be selected from the group consisting of pig heparin binding 39 kDa protein, bovine 39 kDa whey protein, murine breast regressing 39 kDa protein (brp39), human oviduct-specific glycoprotein, murine oviduct-specific glycoprotein, hamster oviduct-specific glycoprotein, bovine oviduct-specific glycoprotein, human chitotriosidase precursor and their fragments.

=> s l12 and "FSKIASNTQ"
L24 1 L12 AND "FSKIASNTQ"

=> d l24 cbib abs

L24 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
1998:785564 Document No. 130:37290 Proteins and novel peptides derived from autoantigen for use in immunotherapy of autoimmune diseases. **Boots, Anna Maria Helena**; Verheijden, Gijsbertus Franciscus Maria; Bos, Ebo Sykren (Akzo Nobel N.V., Neth.). U.S. US 5843449 A 19981201, 19 pp., Cont.-in-part of U.S. 5,736,507. (English). CODEN: USXXAM. APPLICATION: US 1996-634493 19960418. PRIORITY: US 1996-619645 19960325.

AB The present invention relates to novel peptides derived from the autoantigen HC gp-39, said peptides comprising at least one of the amino acid sequences FGRSFTILAS (SEQ ID No. 1), FTLASSETG (SEQ ID No. 2), YDDQESVKS (SEQ ID No. 3) and **FSKIASNTQ** (SEQ ID No. 4). The peptides resemble MHC Class II restricted T-cell epitopes present on the autoantigen HC gp-39 in articular cartilage. HC gp-39, proteins comprising an amino acid sequence which exhibits at least 50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFANISND (SEQ ID No: 10) and said peptides can be used in antigen-specific treatment of articular cartilage destruction in autoimmune diseases in mammals to induce systemic tolerance of the immune system. The autoantigen HC gp-39, proteins comprising an amino acid sequence which exhibits at least 50% homol. with the amino acid sequence YKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFA NISND (SEQ ID NO: 10) and said peptides are also suitable to induce arthritis in animals, preferably mice. The invention furthermore relates to pharmaceutical compns. comprising said autoantigen and/or said peptides, a diagnostic method for the detection of autoreactive T cells in a test sample and test kits to be used in said method. For treating T cell-mediated cartilage destruction disease (e.g. arthritis or **rheumatoid arthritis**), the T cell-specific

tolerance-inducing peptide or protein can also be selected from the group consisting of pig heparin binding 38 kDa protein, bovine 39 kDa whey protein, murine breast regressing 39 kDa protein (brp39), human oviduct-specific glycoprotein, murine oviduct-specific glycoprotein, hamster oviduct-specific glycoprotein, bovine oviduct-specific glycoprotein, human chitotriosidase precursor and their fragments.

=> s l12 and "PTFGRSFTLASSE"
L25 0 L12 AND "PTFGRSFTLASSE"

=> s l12 and "RSFTLASSETGVG"
L26 0 L12 AND "RSFTLASSETGVG"

=> s l12 and "VGYDDQESVKSKV"
L27 0 L12 AND "VGYDDQESVKSKV"

=> s l12 and "SQRFSKIASNTQSR"
L28 0 L12 AND "SQRFSKIASNTQSR"

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	84.44	131.40

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-5.58	-7.44

STN INTERNATIONAL LOGOFF AT 13:24:43 ON 26 AUG 2002